REMARKS/ARGUMENTS

Status of the Claims

Claims 1 to 8, 11 to 18, and 47 to 58 were previously pending. Claims 4 to 6, 11, and 14 to 18 stood withdrawn. Claims 1, 55 and 56 are herein amended and claims 6 and 52 to 54 are canceled without prejudice. Claims 59 to 61 are newly added. After entry of these amendments, claims 1 to 3, 7 to 10, 12, 13, and 47 to 61 will be pending and undergoing examination.

Claims 1 to 3, 7, 8, 12, 13, 47 to 58 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description with respect to the Domain II subject matter.

Claims 1, 7 to 8, 12, 47 to 52, and 55 stand rejected under 35 U.S.C. §102(e) as being anticipated by Cardy et al., U.S. Patent Publication No. 2002/0106370 allegedly having an effective filing date of May 15, 1995.

Claims 52 to 54 stand objected to under 35 U.S.C. §1.75(c) as being in improper dependent claim format.

Claims 55 and 56 stand objected to with respect to various informalities.

Claims 1 to 3 stand rejected for an alleged non-statutory double patenting over claims 1, 4, 6, 11 to 13, 15, 17 to 20 and 42 of the U.S. patent application No. 10/432 ,412 (the '412 application).

Claims 1 to 3, 7 to 8, 12 to 13 and 47 to 55 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

The Applicants respectfully address these grounds for rejection in the order presented in the Office Action.

Amendments to the Claims

Claim 1 and 56 were amended to revert the cell recognition domain back to that set forth in the prior version of the claim. It was also amended to delete a redundant recital. Accordingly, the support for this subject matter is as set forth for the previous versions of these two claims.

New claim 59 depends from claim 1 and sets forth that the ER retention domain comprises the sequence KDEL (SEQ ID NO:13) or REDL (SEQ ID NO:12). Support for this subject matter is found in the specification at page 30, lines 20 to 25.

Claims 55 and 56 were amended as suggested by the Examiner.

New claim 60 depends from claim 1 and sets forth that the amino acid sequence of the ER retention domain is 95% identical to the amino acid sequence of SEQ ID NO:2 spanning amino acid positions from 400 to 613 thereof and that the ER retention domain has a deletion of the amino acid at position 553 of SEQ ID NO:2 and, optionally, a deletion of the lysine at position 613 of SEQ ID NO:2. Support for this subject matter can be found in the specification at page 22, lines 27 to 28, page 30, lines 20 to 21, page 31, third full paragraph. page 31, fourth full paragraph, and page 16, first full paragraph.

Claim 61 sets forth the amino acid at position 279 is an arginine. Support for this subject matter is found *inter alia* in the specification at page 27, lines 13 to 16.

In view of the above, the Applicants believe the amendments to the claims add no new matter and respectfully request their entry.

Response to the rejection of claims 1 to 3, 7, 8, 12, 13, 47 to 58 under 35 U.S.C. §112, first paragraph, for an alleged lack of adequate written description as to the translocation Domain II subject matter.

Applicants would like to first clarify the breadth of the subject matter at issue. The undersigned briefly discussed this rejection with the Examiner in a telephone conference call of September 28, 2006. The undersigned and the Examiner differently construe the following recital of claim 1:

> a translocation domain having an amino acid sequence at least 95% identical to the sequence of *Pseudomonas* exotoxin A (PE) (SEQ ID NO:2) from amino acid position 280 to amino acid position 344 thereof

The Examiner construed the recital of "*an* amino acid sequence at least 95% identical" to be so open so as to embrace subject matter having even only two amino acids in the sequence of SEQ ID NO:2 from position 280 to 344. This position would be correct if the claim recited

> a translocation domain having an amino acid sequence at least 95% identical to **a** sequence of Pseudomonas exotoxin A (PE) (SEQ

> ID NO:2) from amino acid position 280 to amino acid position 344 thereof

However, the claim recites

> a translocation domain having an amino acid sequence at least 95% identical to ***the*** sequence of *Pseudomonas* exotoxin A (PE) (SEQ ID NO:2) from amino acid position 280 to amino acid position 344 thereof

[above bolded italics added for emphasis].

Accordingly, the subject matter at issue is much narrower than that characterized by the Office Action.

The Applicants acknowledge, with regard to the base claim, that the remainder of the translocation domain (i.e., aside from the portion having an amino acid sequence having an amino acid sequence at least 95% identical to the sequence of Pseudomonas exotoxin A (PE) (SEQ ID NO:2) from amino acid position 280 to amino acid position 344 thereof) is 'open'.

Applicants next address the grounds for the rejection. As currently applied, the specification does comply with US patent law for description of a nucleic acid or amino acid sequence. The Federal Circuit court of Appeals addressed the description adequate to show one of skill that the inventors were in possession of a claimed genus at the time of filing. *See, e.g., Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). An applicant may also show that an invention is complete by

> . . . disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Id.* at 1613.

Furthermore, "description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." *See, e.g.*, 66 Fed. Reg. 1099, 1106 (2001). "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify

many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). M.P.E.P. 2163.

As noted previously, the claims provide both structural and functional limitations for the translocation domains. The structure of the polypeptides is recited as a formula, in keeping with the Federal Circuit decision of *Lilly*. The formula recites the sequence of the translocation domain core active site which provides the functional activity. The domain must also exhibit the required functional activity of effecting translocation to the cytosol. Assays for translocation activity are found in the specification, for example at page 32, in the subsection entitled "Translocation to the cytosol." Based on this disclosure, those of skill would be able to both envision the recited translocation domains and assay such domains for the translocation activity required by the claim recitals. Thus, the specification provides written description for the translocation domain subject matter set forth in the claims.

In *Falkner v. Inglis*, No. 05-1324 (Fed. Cir. May 26, 2006) the Federal Circuit ruled that, for claims to nucleic acid sequences and by analogy to amino acid sequences, absence of examples does not render written description inadequate and that actual reduction to practice is not required. *See, e.g.*, *Falkner* slip op at page 14. The court also ruled that publicly available references that describe essential regions of a pox virus could be used to allow those of skill to choose an essential vaccinia gene and then to make a claimed virus. *See, e.g.*, *Falkner* slip op at page 13. In the present case, Applicants have identified the pertinent functionally important region of SEQ ID NO:2 to assist those of skill in designing functional polypeptides with 95% identity to this region.

Additionally, one of ordinary skill in the art would readily appreciate that variant functional domains could be readily be obtained by use of conservative amino acid substitutions. Applicants respectfully note that such is disclosed in the specification at page 15, lines 16 to 24.

Turning to Example 14 of the *Synopsis of Application of Written Description Guidelines*, the Applicants note that the Example concerns a disclosure which teaches the full length of a protein, the function of that protein, and how to assay for it. The disclosure does not exemplify any variants of the protein and does not introduce any supportive prior art teachings.

The Examiner would distinguish the present facts from the above Example on the grounds that the Example concerned a full length protein having a specific function whereas the present Applicants' translocation domain concerns only a portion of a polypeptide domain having a recited function. Applicants respectfully submit that this is distinction without a difference. Both concern a polypeptide sequence having a specified amino acid sequence, a disclosed activity, and disclosed methods for identifying that activity.

Applicants further invite the Examiner's attention to the *Sun* decision by the Board of Patent Appeals and Interferences (see, *Ex parte Sun*, Appeal No. 2003-1993 on Application No. 09/470,526). In *Sun,* the Board considered a claim to a polynucleotide sequence having 80% identity to the entire coding region of a disclosed polynucleotide sequence. The *Sun* Applicants had not disclosed a single representative species with 80% identity and the recited function. The Examiner in *Sun* had argued that the specification did not teach a single variant with the pertinent function. The Board did not find the fact that the specification does not specifically teach the structure of a species with 80% identity and the WEE1 function to be dispositive of the written description question. Rather, the Board looked to the teachings of the prior art and concluded in view of those teachings that one of ordinary skill in the art would have recognized that the Applicants were in possession of the claimed subject matter.

Accordingly, Applicants respectfully invite the Examiner's attention again to the publicly available Kasturi et al. reference. This reference disclosed about 19 mostly non-conservative substitutions with alanine at 19 positions in Exotoxin A domain II from positions 280 to 344. They found 3 such substitutions which rendered the Exotoxin A inactive and 16 which retained at least some activity including four substitutions being as active or more active than the native Exotoxin A (*see*, Table VI at p. 23433 of Kasturi et al.). This reference does not merely exemplify alanine substitutions as suggested by the Office Action, rather it strongly evidences that the translocation domain region at issue is robust to even non-conservative amino acid substitutions. In this regard, Applicants further note that Jinno et al., *JBC* 264 (27):15953 (1989)(already of record) is in accord in showing that even non-conservative substitutions in the pertinent sequence are well-tolerated. Jinno in Table V at page 15957 shows that substitutions of glycine for arginine in the five arginine residues falling in this region results in translocation

domains with substantial activity in three of five positions. Accordingly, in view of such teachings, one of ordinary skill in the art would certainly appreciate that the Applicants were in possession of the recited translocation domain subject matter at the time the application was filed.

Accordingly, the Applicants respectfully request reconsideration and withdrawal of the rejection for alleged lack of written description.

Response to the rejection of claims 1, 7 to 8, 12, 47 to 52, and 55 for alleged anticipation by Cardy et al., U.S. Patent Publication No. 2002/0106370 (the Cardy reference).

Pursuant to the MPEP §2136, the Applicants believe this Cardy reference is not available as 102(e) art as of its international filing date as alleged in the Office Action. Cardy et al. enjoys an international filing date of May 15, 1995. However, MPEP §2136 and MPEP §2136.03 set forth that published U.S. patent application or U.S. patent references claiming priority benefit of an international applications filed on or *after* November 29, 2000 may be available as a reference under 35 U.S.C. §102(e) as of their international filing dates. In view of its *pre*-November 29, 1999 filing date, this Cardy reference does not appear to qualify as 35 U.S.C. §102(e) art as of its international filing date.

Not withstanding the above and noting that the corresponding PCT application (enclosed) was published as WO/95/31483 on 23 November 1995, Applicants proceed to address the substantive issues represented by the Examiner's use of this Cardy art. For both our conveniences, in referencing the teachings of the Cardy disclosure, the Applicants will rely upon the specification of the cited U.S. Patent Publication No. 2002/0106370 as this publication appears to be identical to that of WO/95/31483 and has the advantage of having numbered paragraphs.

Pursuant to MPEP §2131, to anticipate a claim the reference must teach every element of the claim:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ...claim." Richardson v.

> Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an ipsissimis verbis test, i.e., identity of terminology is not required. In re Bond, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). ...

Applicants further note that the Examiner is proceeding on a theory of inherency. With regard to anticipation under a theory of inherency, the MPEP states:

> "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *See,* MPEP § 2112 (emphasis in original), quoting *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *See,* MPEP § 2112, quoting *In re Robertson* 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Furthermore, "[i]n relying upon a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *See,* MPEP § 2112 (emphasis in original), quoting *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

The Office Action contends that Cardy discloses locating the cysteine to cysteine loop containing an epitope of a pathogen between the translocation domain and the endoplasmic reticulum retention domain. To support this contention, the Office Action principally relies upon Figure 10 and the other figures of the Cardy reference. However, Figure 10 sets forth a *generic* translocation domain and *not* the translocation domain set forth in the Applicants' claims and *none* of the other eight figures are actually described in the specification as necessarily having *any* translocation domain. The descriptions of the first 9 drawings refer to immunodominant peptide domains and make *no* mention of a translocation domain (*see* Cardy, description of the figures on page 3). Additionally, where a translocation may be used according to Cardy, that reference describes a number of translocation domains as being suitable, in addition to the Pseudomonas exotoxin translocation domain (see, page 2, middle of paragraph 13). Cardy also teaches using antibodies directed toward an internalizing antigen in the last sentence of paragraph 15. There is simply *no* support for the implicit position adopted by the Office Action

that the figures in the specification indicate that the translocation domain of Figure 10 is *necessarily* a Pseudomonas exotoxin A translocation domain.

Moreover, assuming *arguendo* that the translocation domain were that of Pseudomonas exotoxin A, there is simply no support for the position adopted by the Office Action that the figures in the specification indicate that the cell binding domain ought to be placed before the translocation domain of Figure 10. In fact, Figure 10 is not agnostic about its location within the Cardy chimera. Figure 10 clearly shows lines leading from the translocation domain and the endoplasmic reticulum domain. These lines may be fairly construed as requiring or allowing other portions of the chimera to precede and follow the depicted portions. The specification does not cure the deficiency represented by the figures, but adds to it. At paragraph 15, the Cardy specification states "It will be understood by those skilled in the art that immunodominant peptides might be included at many different locations in an antibody molecule using recombinant DNA." The specification even contemplates inserting immunodominant peptides into the complementarity determining region of the antibody in the last sentence of paragraph 15.

Additionally, with regard to the base claim, assuming *arguendo* even further that Cardy, either in its text or figures or both, did disclose a chimera having a cell recognition domain, translocation domain, immunodominant peptide domain and an endoplasmic reticulum retention domain placed in that specific order, Cardy does not set forth that the immunodominant peptide domain ought to consist essentially of one immunodominant peptide and that it should be a cysteine-cysteine loop wherein the loop encodes an epitope of a pathogen non-native to PE domain Ib. Ignoring that Figure 10 actually sets forth a plurality of immunodominant peptides in the depicted domain, the mere possibility that such an epitope, if selected, might be placed there as a single epitope domain is still simply not enough to negate novelty on a theory of inherency.

Additionally, with regard to claim 56, the Applicants note that the instant claim sets forth the epitope is located within domain Ib of pseudomonas exotoxin A in place of amino acid residues 372 to 379, inclusive, of SEQ ID NO:2. Cardy makes no mention of domain 1b of Pseudomonas exotoxin A or further that their immunodominant peptide domains could be inserted therein as set forth in the claim. Cardy mentions the translocation domain of

Pseudomonoas exotoxin as one of a number of possible translocation domains. This domain does not embrace domain 1b. Therefore, in Figure 10, there is no domain 1b or portion of domain 1b and no cysteine residues of domain 1b, or basis for asserting that the Cardy *multiple* peptide domains of Figure 10 are necessarily so placed between such cysteine residues of domain 1b. Cardy does not disclose all the elements of the Applicants claims even under a theory of inherency. Again, the recited subject matter simply does not necessarily flow from the Cardy disclosure.

As Cardy neither discloses the identical invention in as complete detail as is contained in a claim nor discloses the same arrangement of elements as set forth in a claim, either expressly, or particularly under a theory of inherency, the Applicants respectfully request that the above ground for rejection be reconsidered and withdrawn.

Response to the objection to claims 52 to 54 for an alleged improper dependent claim format and to the objection to claims 55 and 56 for various informalities.

Acknowledging for the record that the recitals of comprising in the base claim are 'open' and without acquiescing to the position of the Examiner on the merits, and in order to expedite prosecution of the application, the Applicants have canceled claims 52 to 54. In addition, the Applicants have amended claims 55 and 56 as suggested by the Examiner.

In view of the above, the Applicants respectfully request that the above rejections be withdrawn.

Response to the rejection of claims 1 to 3 for alleged non-statutory double patenting over claims 1, 4, 6, 11 to 13, 15, 17 to 20 and 42 of the '412 application.

The allowance in the '412 application has been withdrawn and the application remains under examination. Accordingly, the Applicants refer the Examiner to MPEP §804 which sets forth at p. 800-17 the procedure to be followed with respect to such provisional rejections:

> B. Between Copending Applications-Provisional Rejections
>
> Occasionally, the examiner becomes aware of two copending applications >that were< filed by the same inventive entity, or by different inventive entities having a common

> inventor, and/or by a common assignee >, or that claim an invention resulting from activities undertaken within the scope of a joint research agreement as defined in 35 U.S.C. 103(c)(2) and (3),< that would raise an issue of double patenting if one of the applications became a patent. Where this issue can be addressed without violating the confidential status of applications (35 U.S.C. 122), the courts have sanctioned the practice of making applicant aware of the potential double patenting problem if one of the applications became a patent by permitting the examiner to make a "provisional" rejection on the ground of double patenting. In re Mott, 539 F.2d 1291, 190 USPQ 536 (CCPA 1976); In re Wetterau, 356 F.2d 556, 148 USPQ 499 (CCPA 1966). The merits of such a provisional rejection can be addressed by both the applicant and the examiner without waiting for the first patent to issue.
>
> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in >at least< one of the applications.
> **
>
> 1. Nonstatutory Double Patenting Rejections
>
> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. If the ODP rejection is the only rejection remaining in the later-filed application, while the earlier-filed application is rejectable on other grounds, a terminal disclaimer must be required in the later-filed application before the rejection can be withdrawn.
>
> If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue. If both applications are filed on the same day, the examiner should determine which application claims the base invention and which application claims the improvement (added limitations). The ODP rejection in the base application can be withdrawn without a terminal disclaimer, while the ODP rejection in the improvement application cannot be withdrawn without a terminal disclaimer.

The present application enjoys an earlier priority date than the '412 application. Accordingly, Applicants believe that once the present application is otherwise deemed to be in

allowable condition, it would be proper given the recent disallowance of the '412 application for the Examiner to withdraw the provisional double patenting rejection in the present application and allow the application to proceed to issue. The merits of any double patenting concern can be addressed to the satisfaction of the Examiner in the co-pending application when it comes up for examination. Holding the double patenting rejection in abeyance is in accord with USPTO procedure and will expedite the prosecution of the present application.

Response to the rejection of Claims 1 to 3, 7 to 8, 12 to 13 and 47 to 55 as allegedly failing to comply with the written description requirement.

Without acquiescing on the merits, the Applicants have amended the base claim to set forth the cell recognition domain subject matter as set forth in the previous version of the base claim. Accordingly, the Applicants respectfully request that this grounds of rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

Frank J. Mycroft
Reg. No. 46,946

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300

Attachments
FJM:kar
60902479 v1